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PERSPECTIVE

Elevated bone mass: a weighty matter?

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Introduction

Osteoporosis is recognized to be a major public health problem with a significant population burden related to fracture morbidity, excess mortality, and health care expenses. Moreover, the case-fatality rate for hip fractures can exceed 20% [1, 2], and other osteoporosis related fractures can lead to significant long-term disability and decreased quality of life [3, 4]. Up to 16% of women and 7% of men over the age of 50 are affected [5]. The number of fracture sufferers worldwide in 2000 was estimated at 56 million, with approximately 9 million new osteoporotic fractures occurring each year [6], and this is projected to increase markedly over the next few decades as the number of elderly individuals increases [7].

The two key features of osteoporosis are a reduction in skeletal strength [largely determined by bone mineral density (BMD)] and a consequent increase in risk for spontaneous and minimal trauma (fragility) fractures [8, 9]. In the absence of a fracture history, osteoporosis is operationally defined as BMD of the lumbar spine, proximal femur, or distal forearm derived from dual energy X-ray absorptiometry (DXA) that is 2.5 standard deviations (SD) or more below average for a young adult (T-score) [8]. Under the original World Health Organization (WHO) formulation, this concept was only applicable to post-menopausal Caucasian women. Since then, the formulation has been extended to also apply to other ethnic groups and men age 50 or older, with the additional clarification that *T*-score should be calculated using a standardized reference population [Caucasian woman from the National Health and Nutritional Evaluation Survey III (NHANES) for hip measurements] [10].

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Elevated bone mass

Against this backdrop on the risks of low bone density, there has been recent interest in elevated bone mass as a finding of scientific and clinical interest. This presumes that artifactual causes for elevated BMD (such as degenerative or post-surgical changes) have been excluded. Although firm definitions do not exist, some operationally define unusually high BMD as a *T*-score that is +2.5 or higher or an age- and sex-matched *Z*-score that is +2 or higher [11]. Based upon an assumption of a normal (Gaussian) distribution, high BMD should be infrequent (*T*-score +2.5 or higher expected in 0.6% of healthy young adults and only 0.003% of 80-year olds) [12]. Nonetheless, when individuals with unusually high BMD are encountered in clinical practice, questions arise over whether this is a marker for systemic or skeletal disease that requires investigation. There are a large number of causes for elevated BMD [13], and some of these (e.g., infection with hepatitis C) are important to diagnose and treat. The single most common finding in individuals with elevated bone mass is overweight [14, 15], and this offers insights into the factors that help to regulate bone mass and calcium economy.

The scientific community has been interested in unexplained high BMD, especially when this affects kindred, thereby suggesting a familial (genetic) basis. The classical example is osteopetrosis, a heterogeneous group of rare genetic disorders resulting in osteoclast failure that are associated with a parodoxical increase in fractures [16].

Other conditions lead to high bone mass that is protective against fractures. For example, gain-of-function mutations of the gene coding for lipoprotein related peptide 5 (LRP-5) gives a phenotype of high BMD, thickened mandible, and torus palatinus (in contrast to osteoporosis–pseudoglioma syndrome that results from a loss-of-function mutation in the same gene). Deletion mutations in the gene-encoding sclerostin produces osteosclerosis and is known as Van Buchem syndrome. These latter have been linked to the pathway regulating the biologic activity of the osteoblast, which is responsible for new bone formation. The canonical *Wnt* signaling system integrates LRP-5 (a coreceptor for *Wnt*), sclerostin (a natural inhibitor of LRP-5), beta-catenin (which regulates nuclear transcription of target genes after stabilization by *Wnt*), and several other regulators of osteoblast activity (reviewed by Baron et al. [17]). These human experiments of nature, replicated in laboratory animals, have made enormous contributions to understanding the basic biology of bone formation and may help to define new molecular targets for intervention.

Low BMD and low BMI

Screening strategies to identify at risk individuals with low BMD prior to fracture have been proposed. Mass screening with DXA of women age 65 years and older without other risk factors was recommended by the United States Preventive Services Task Force (USPSTF) in 2002 (grade B) [18, 19]. More recently, an American College of Physicians evidence-based guideline identified age 70 years and older as a significant risk factor for fracture in men by (grade B) [20]. In contrast to this approach, others advocate more selective testing (targeted case finding) and use of simple screening tools based upon clinical risk factors to identify individuals at risk for low BMD and, conversely, those that do not require DXA testing. Body weight and body mass index (BMI) have been shown to explain an important proportion of the variance in BMD (8.9–19.8% of total variance) with correlations in the order of r=0.3–0.6 [21, 22]. Systematic reviews have noted the strong correlation between low BMD and low body weight (and BMI) in postmenopausal women, perimenopausal women, and older men [20, 23, 24]. It is, therefore, not surprising that virtually all screening tools include weight or BMI. In the simplest system, the National Osteoporosis Foundation uses weight less than 127 lbs (58 kg) as a single criterion for DXA testing in menopausal women [25]. Other models include weight and age together (Osteoporosis Self-Assessment Tool, OST [26]) or various combinations of age, weight, and other clinical risk factors (fracture history, estrogen therapy, ethnicity, smoking, rheumatoid arthritis, and family history) [27]. A direct comparison of several instruments in a large population-based cohort of 7,779 US white women age 67 years and older concluded that weight identified low BMD as accurately as more complex risk assessment tools [28], supporting the use of simple weight cut points in an osteoporosis screening protocol for elderly women.

A logical extension of the above is to use body mass in addition to other variables to predict fractures. At first glance, it may seem obvious that factors associated with low bone density will also predict fractures, but this is not necessarily the case. DXA is a two-dimensional (projectional) technology that measures areal BMD (in unit g/cm^2) rather than "true" volumetric BMD (in unit g/cm^3). As a result, individuals with identical material (volumetric) BMD will demonstrate different *T*-scores (based upon the areal BMD) if skeletal sizes are different, with lower *T*-scores in those with smaller skeletal size. Paradoxically, skeletal size increases with aging due to periosteal bone apposition (notwithstanding the higher fracture rates in older individuals), taller peak adult height is a risk factor for hip fracture (despite taller height being a proxy for a larger skeletal size), and Asians have lower rates of hip fracture than Whites despite lower BMD (at least partially related to the smaller skeletal size of Asians) [29–32]. Indeed, one recent report found that OST has reasonably good performance for identifying low BMD in 8,254 women age 40–59 years but was poor for fracture discrimination [33].

The ability to accurately gauge fracture risk is critical in identifying cost-effective thresholds for intervention [34, 35]. The WHO Collaborating Centre has recently identified a set of seven clinical risk factors (BMI, prior fragility fracture, a parental history of hip fracture, smoking, use of systemic corticosteroids, excess alcohol intake, and rheumatoid arthritis), which in addition to age and sex contribute to fracture risk independent of BMD [35, 36]. A 10-year fracture risk assessment tool (FRAX™) is available online at http://www.shef.ac.uk/FRAX/. Based upon a pooled analysis from 12 large cohorts, BMI was found to have reasonable performance for fracture prediction when BMD was unknown [35, 37]. Without information on BMD, the age-adjusted risk for hip fracture increased by 7% (95% CI, 6–9%) for each unit decrease in BMI, and this effect was similar in men and women. All other factors being equal, a BMI of 20 kg/m^2 nearly doubled the risk of hip fracture compared with a BMI of 25 kg/m^2, but excess weight was not equally protective as a BMI of 30 kg/m^2 reduced hip fracture risk by only 17% compared with BMI 25 kg/m^2. Since BMI and BMD are closely correlated, there is considerable attenuation of the contribution of BMI in fracture prediction when BMD is known. Thus, BMI may have a particular value in prescreening individuals for DXA or as a proxy for BMD in

countries that do not have good access to this technology. One interesting observation with the FRAX tool is that a 10-year fracture risk shows a non-linear (inverted U) relationship with BMI. Fracture risk peaks when BMI is approximately 25 kg/m^2 and is lower with higher or lower BMI. At first glance, this may appear to be counter-intuitive, since fracture rates should *increase* with lower BMI, but this reflects competing mortality in underweight individuals such that they have fewer years of expected lifetime during which fractures can occur.

High BMD and high BMI

As noted earlier, most work has focused on the association between low BMD and low BMI. However, there is a strong linear correlation between these two parameters across the range spectrum. Therefore, it is plausible that high BMD would be associated with high BMI. Indeed, this has been reported in two studies to date. Pesonen et al. [38] have documented that younger women with a BMI over 30 kg/m^2 predicted a sixfold increase in the risk of high BMD. In this study, women with high BMD sustained fewer fractures than the control group. A subsequent report looked at a clinical cohort of 16,500 women age 50 years and older and again found a strong correlation between body mass (weight or BMI) and BMD of the lumbar spine and the proximal femur) [15]. Elevated BMD (defined as *T*-score +2.5 or higher) or *Z*-score (+2.0 or higher) was largely explained from higher BMI. In fact, the majority of individuals with high BMD had a BMI in the obese range (30 kg/m^2 or greater). Fracture outcomes were assessed using linkage to administrative data sources, and there was no evidence that high BMD was associated with an increase in fracture risk. This study was unable to identify other potential diagnoses that might affect BMD, however.

Body mass and bone metabolism

The factors that link bone metabolism and body mass are not fully defined. Broadly, they can be considered under the headings of (a) technical, (b) passive actions of weight, (c) direct actions of muscle, and (d) indirect actions of fat.

Differential effects of body composition on X-ray attenuation complicate assessment of BMD measurement with DXA and may, in part, contribute to the correlation between body mass and BMD. DXA assumes that the body consists of two compartments, a bone compartment and a soft tissue compartment. Instruments are calibrated based upon the known physical attenuation of X-rays by calcium. The soft tissue attenuation value is derived from bone-free pixels in order to accommodate individual variation in body composition, as there are small differences in fat and lean X-ray attenuation values. This procedure works reasonably well for individuals of average body composition, but may be inadequate for extremes of body fatness or leanness or where there is non-uniform fat distribution adjacent to or within bone [39]. Although a detailed discussion is beyond the scope of this review, it has been estimated that DXA can have accuracy errors up to 1 standard deviation (a *T*-score unit) primarily due to the effects of non-uniform fat distribution [40]. Caution has therefore been urged in interpreting apparent changes in BMD when there are large simultaneous changes in body composition (>10% body weight), such as rapid weight loss from bariatric surgery [41]. Bone marrow fat behaves differently from body fat (visceral and subcutaneous), with an age-related decrease in the former while the latter increases [42]. DXA cannot identify these discordant changes in intraosseous and extraossesous soft tissue composition, and therefore, it is not possible to predict whether BMD will be overestimated or underestimated. Although there is no debate that corticosteroid therapy is a risk factor for osteoporosis and fractures, the effect of corticosteroids on intraosseous fat has been identified as an additional factor that may confound assessment of BMD change since an increase of intraosseous fat would result in underestimation in BMD. Notwithstanding the aforementioned concerns, the observation that body mass is also strongly associated with BMD at peripheral skeletal sites, such as the radius and calcaneus where intraosseous fat distribution shows much less variability, underscores a strong biologic relationship between weight and BMD that cannot be attributed to technical factors.

There has been an ongoing debate over the relative importance of the passive skeletal loading versus active muscular contraction that occurs in heavier individuals [43]. The relative importance of lean versus fat mass is difficult to disentangle, since obese individuals also have an increase in absolute lean mass, presumably an adaptive response that maintains mobility. Most studies show that, when lean and fat mass are considered simultaneously, the former shows a strong positive correlation with BMD, whereas the latter is neutral or even negatively correlated [44–47]. This would tend to support the importance of dynamic skeletal loading over passive loading. Not all studies are in agreement, however, and Reid et al. [48] has found that in menopausal women fat mass may be more important than lean mass. Fat mass may be more important in menopausal women than in men or younger women due to its role in peripheral aromatization of estrogen. Large cohort studies have shown that low levels of endogenous estrogen in menopausal women may be physiologically relevant in the maintenance of BMD and protection against fractures [49, 50].

Alternatively, adipocyte-derived cytokines (adipocytokines) may play a role in bone mass regulation (recent reviewed by Zhao et al. [51] and Reid [43]). Leptin and resistin increase when there is greater fat mass, whereas adiponectin is decreased. It is still unclear whether these humoral factors have direct or indirect effects on bone mass. Obesity has been identified to be a pro-inflammatory state with an increase in C-reactive protein, adiponectin, tumor necrosis factor-alpha, resistin, and interleukins [52]. Systemic inflammation has been associated with reduced BMD in some studies [53, 54]. More recently, the concept of "lipotoxicity" has emerged as a factor that may contribute to osteoporosis [42]. Osteoblasts and adipocytes are derived from a common mesenchymal stem cells, and aging leads to a shift in stem cell differentiation from osteoblasts to adipocytes. It has been proposed that progressive infiltration of bone marrow by fat results in paracrine secretion of toxic fatty acids and cytokines that reduce osteoblast action and survival while promoting osteoclast differentiation and bone resorption [42]. Therefore, fat mass could have a direct inhibitory effect on bone mass through multiple mechanisms. Defining the interplay and relative importance of these mechanisms awaits further investigation.

Clinical considerations

The primary purpose of BMD assessment is for the diagnosis of osteoporosis and assessment of fracture risk. Some disorders associated with high BMD (such as osteopetrosis and pyknodysostosis) show a paradoxical increase in fracture risk. However, most of the other disorders appear to result in structurally competent bone, and this appears to be the case for high BMD that occurs in the setting of an elevated BMI. Although the frequency of individual disorders resulting in high BMD is quite low, collectively, they are important, since some of them warrant specific treatment. An investigation plan that maximizes yield and minimizes cost is needed.

There are currently more questions than answers about the frequency and causes of elevated bone mass. Extensively investigating high BMD in obese patients without a fracture history is unlikely to be productive or a good use of health care resources. On the other hand, it is important not to ignore unexplained high BMD, since this has the potential to provide insights into basic skeletal physiology by uncovering new regulators of bone mass. As in all things, the challenge is to find the right balance.

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